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Stereoselective Synthesis of Trifluoromethyl Analogues of Polyhydroxypyrrolidines

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Incorporation of fluorine atoms into organic molecules significantly enhances many of their properties, such as solubility, metabolic stability, and bioavailability. Among organofluorine molecules, trifluoromethylated compounds play a unique and important role in agricultural and medicinal chemistry. An efficient strategy for the synthesis of a variety of trifluoromethylated polyhydroxypyrrolidines is described. This strategy involves a diastereoselective nucleophilic addition reaciton of trimethyl(trifluoromethyl)silane to sugar-derived cyclic nitrones followed by reductive N–O bond cleavage and removal of benzyl groups.

Introduction

Pyrrolidines are commonly found subunits present in many natural products, especially alkaloids (Figure 1), which have been isolated from natural sources, including plants and microorganisms.[1] These compounds have been shown to exhibit potent and selective inhibitory activities against biologically-important enzymes such as glycosidases and other enzymes closely associated with the metabolism of *N*-linked glycoproteins.[2] Owing to this biological activity, iminocyclitols have potential to become powerful tools against cancer,[3] viral infections,[4] diabetes[5] and lysosomal storage disorders, and are consequently considered privileged scaffolds for drug design.[6] An unusual variety of natural polyhydroxylated pyrrolidines possessing a methyl group at C-2 of the pyrrolidine system have recently attracted a lot of attention from both synthetic and medicinal chemists. Among these compounds, codonopsine (**1**) and codonopsinine (**2**) were isolated[7] from *Codonopsis clematidea*, and 3,4-dihydroxy-2-hydroxymethyl-6-methylpyrrolidine [6-deoxy-DMDP (**3**); an inhibitor of β-mannosidase, β-galactosidase, and α-fucosidase] was isolated from *Angylocalyx* sp. Leguminosae (Figure 1).[8]

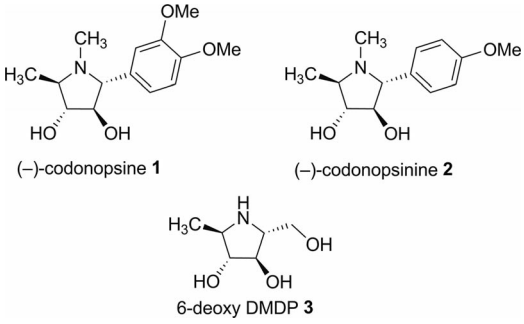

Figure 1. Different polyhydroxypyrrolidine natural products.

Likewise, amines bearing a trifluoromethyl group at the α-position constitute an important class of biologically active compounds (Figure 2).[9] The strong electron-withdrawing nature and large hydrophobic domain of the trifluoromethyl group can significantly influence the basicity and solubility of amines, thereby modifying the bioavail-

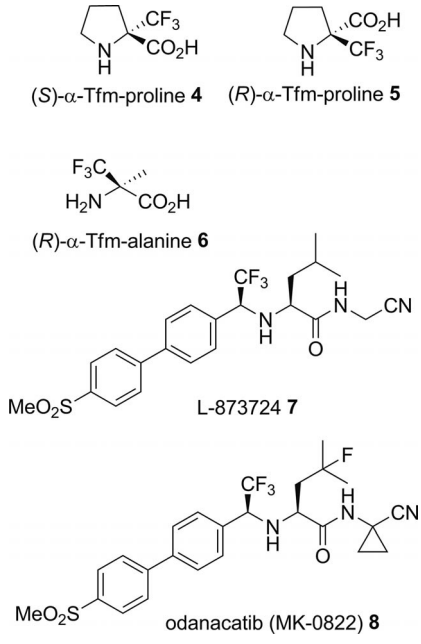

Figure 2. Trifluoromethylated amines as natural products.

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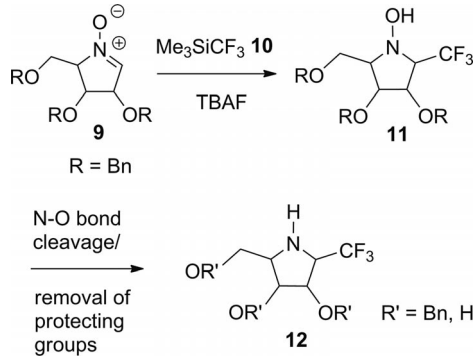
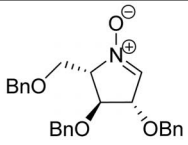
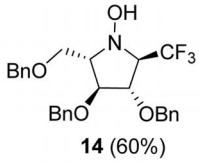
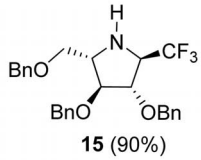
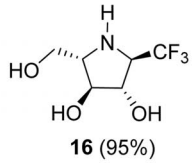
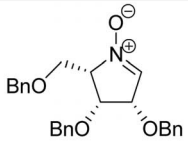
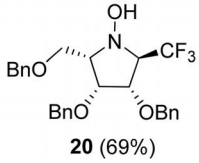
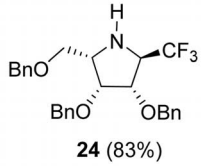
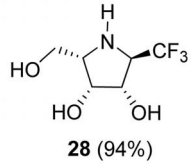
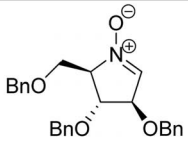
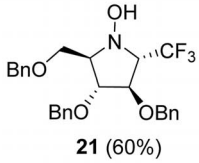
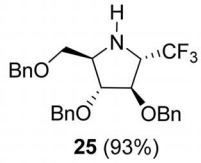
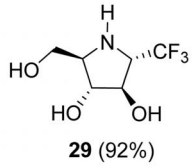
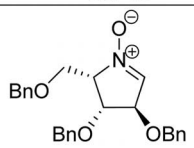
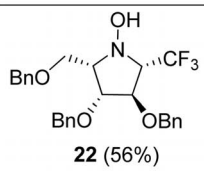
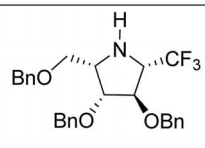
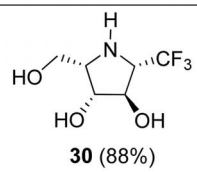
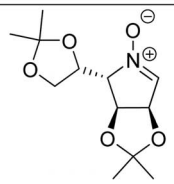
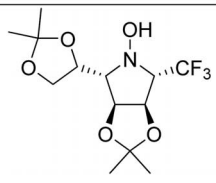
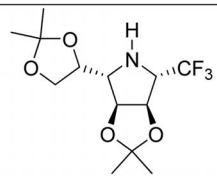
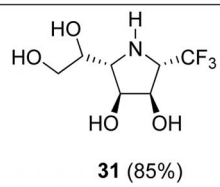
ability and stability of target drugs. For these reasons, they have become popular and essential building blocks in the design and synthesis of fungicides, pesticides, insecticides, selective antibacterial agents, enzyme inhibitors, and enzyme receptor antagonists or agonists.[10] As part of our studies on sugar-derived cyclic nitrones[11] and fluorinated compounds,[12] we developed an interest in synthesizing chiral trifluoromethylated analogues of 6-deoxy-DMDP (**3**). We intended to take advantage of the availability of a set of protected hydroxylated cyclic nitrones that can easily be prepared from carbohydrates, thus providing one or more stereogenic centers of the pyrrolidine ring (Scheme 1). Furthermore, several polyhydroxypyrrolidine alkaloids have been synthesized through diastereoselective nucleophilic addition reaction of organometallic reagents to sugar-derived cyclic nitrones.[13]



Scheme 1. Nucleophilic addition reaction of Me_3SiCF_3 to sugar-derived cyclic nitrones followed by N–O bond cleavage and removal of protecting groups.

To introduce the trifluoromethyl group trimethyl(trifluoromethyl)silane (Ruppert–Prakash's reagent)[14] was used, because it has been widely used for trifluoromethylation of aldehydes and ketones, enones and indinones, porphyrins, chlorins and bacteriochlorins, carbohydrates, esters, sulfonic, sulfinic and selenic esters and α-keto esters, amino esters, oxazolidinones, amides and α-keto amides, imines,

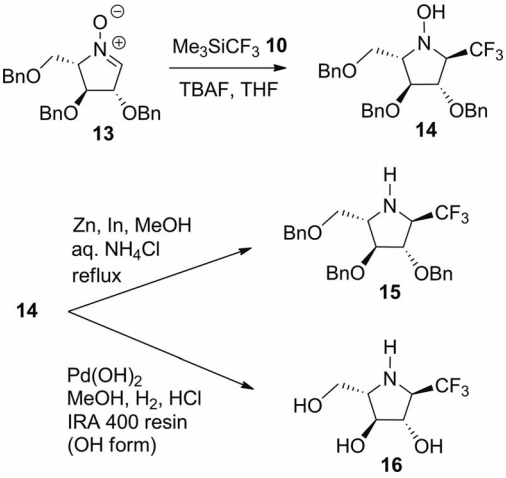
Table 1. Nucleophilic addition reaction of Me_3SiCF_3 to different sugar-derived cyclic nitrones followed by N–O bond cleavage and removal of protecting groups.

Sugar-derived cyclic nitrones	Nucleophilic addition of Me_3SiCF_3[a]	Reductive N-O bond cleavage[b]	Removal of protecting groups[c]
 **13**	 **14** (60%)	 **15** (90%)	 **16** (95%)
 **17**	 **20** (69%)	 **24** (83%)	 **28** (94%)
 *ent*-**13**	 **21** (60%)	 **25** (93%)	 **29** (92%)
 **18**	 **22** (56%)	 **26** (86%)	 **30** (88%)
 **19**	 **23** (63%)	 **27** (77%)	 **31** (85%)

[a] Trifluoromethylated cyclic hydroxylamines were synthesized from the respective cyclic nitrones and Me_3SiCF_3 by using TBAF in THF at 0 °C. [b] Trifluoromethylated amines were synthesized from the respective trifluoromethylated cyclic hydroxylamines by using Zn, In, aq. NH_4Cl, MeOH, reflux, 12 h. [c] Trifluoromethylated polyhydroxypyrrolidines were synthesized through removal of protecting groups.

thiocyanate and selenocyanate, and organophosphorus compounds.[15] However, little attention has been paid to the trifluoromethylation of nitrones.[16]

We started to explore its reactions with electrophilic sugar-derived cyclic nitrones (**13**, *ent*-**13**, and **17**–**19**) in the hope of finding new ways of introducing a CF_3 group stereoselectively into a pyrrolidine ring. To begin with, D-xylose-derived cyclic nitrone **13** was examined as a model substrate for direct trifluoromethylation. When a mixture of **13**, Me_3SiCF_3 (**10**; 1.0 equiv.), and tetra-*n*-butylammonium fluoride (TBAF; 1.5 equiv.) in tetrahydrofuran (THF) was stirred at 0 °C under a nitrogen atmosphere for 30 min, desired product **14** was formed in 60% yield (Scheme 2). It is worth mentioning that product **14** resulted from *anti* attack of the trifluoromethyl anion with respect to the 4-benzyloxy group as a result of both steric and stereoelectronic effects.[17]



Scheme 2. Nucleophilic addition reaction of Me_3SiCF_3 to D-xylose-derived cyclic nitrone followed by N–O bond cleavage and removal of benzyl groups.

Next we turned our attention to transform cyclic hydroxylamine **14** into corresponding trifluoromethylated amine **15** through cleavage of the N–O bond. Under standard conditions,[18] Zn dust and indium powder in aq. NH_4Cl and MeOH at reflux temperatures for 12 h, smoothly cleaved the N–O bond and provided desired product **15** in 90% yield (Table 1).

Finally, removal of the benzyl groups was achieved by treating with 10% $Pd(OH)_2/C$ (Pearlman's catalyst) in MeOH/HCl under a hydrogen atmosphere[19] from compound **14** to afford trifluoromethylated polyhydroxylated pyrrolidine **16** as its salt, which was later neutralized with IRA-400 resin (OH^- form; Scheme 2).

To investigate the substrate scope, we then performed a series of reactions of various sugar-derived cyclic nitrones with Me_3SiCF_3 (Table 1). Gratifyingly, nitrone **17**, *ent*-**13**, **18** and **19** on treatment with Me_3SiCF_3 (**10**), furnished trifluoromethylated cyclic hydroxylamines **20**–**23** in good yields (69, 60, 56 and 63%, respectively; Table 1). Having successfully synthesized a variety of sugar-derived trifluoromethylated cyclic hydroxylamines, these intermediates were subsequently converted into corresponding trifluoromethylated amines **24**–**27** through cleavage of the N–O bond.

Removal of the protecting groups was performed on sugar-derived trifluoromethylated cyclic hydroxylamines **20**–**22** to obtain trifluoromethylated polyhydroxylated pyrrolidines **28**–**30**. In the case of compound **27** deprotection of acetonide groups was carried out in 6 N HCl in MeOH to obtain trifluoromethylated polyhydroxylated pyrrolidine **31** in 85% yield.

Conclusions

In summary, we have illustrated a simple and efficient route to sugar-based trifluoromethylated cyclic hydroxylamines by using a nucleophilic trifluoromethylation reaction of sugar-derived cyclic nitrones with Ruppert's reagent, Me_3SiCF_3, in the key step. Subsequently, upon reductive N–O bond cleavage and removal of the protecting groups these compounds afforded trifluoromethylated analogues of the natural product 6-deoxy-DMDP. The introduction of a trifluoromethyl group may significantly improve the bioavailability of polyhydroxylated pyrrolidines.

Experimental Section

General Methods: Unless otherwise noted, all the starting materials and reagents were obtained from commercial suppliers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl, and toluene from sodium. Dichloromethane, hexane and acetonitrile were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Air and moisture sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Flash chromatography was performed by using silica gel (100–200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) by using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotations were recorded with a Rudolph Autopol IV digital polarimeter. High-resolution mass spectra (HRMS) were recorded on a micromass ESI TOF (time of flight) mass spectrometer. IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AV 400 MHz instrument in $CDCl_3$, D_2O and CD_3OD. The following abbreviations are used in reporting NMR spectroscopic data: s, singlet; br., broad; d, doublet; t, triplet; q, quartet; dd, dt, doublet of triplets; td, triplet of doublets; ABq, AB quartet; m, multiplet all of the reported ^{19}F NMR spectra were recorded with hydrogen decoupling. For compounds **14**–**15**, **20**–**22** and **24**–**26** CF_3 peaks were not observed on the ^{13}C NMR spectra owing to the dilute samples.

General Procedure for the Nucleophilic Addition of Me_3SiCF_3: To a stirred solution of nitrone (1 mmol) in dry THF (15 mL) was added trimethyl(trifluoromethyl)silane (1 mmol) and the mixture was cooled to 0 °C. Then, a solution of TBAF (1.5 mmol) in THF (4 mL) was added, and the obtained mixture was stirred at room temperature for 0.5 h. The completion of the reaction was confirmed by TLC. After completion of the reaction, the mixture was treated with dilute aqueous HCl, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The com-

bined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated under vacuum to obtain the crude product, which was purified by silica gel flash column chromatography.

(2*S*,3*S*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrroli-din-1-ol (14): Following the general procedure, starting from nitrone **13** (50 mg, 0.12 mmol) and trimethyl(trifluoromethyl)silane (**10**; 17 mg, 0.12 mmol), product **14** was obtained as a colorless oil (35 mg, 60%) after purification by silica gel column chromatography (12% ethyl acetate/hexanes). R_f = 0.6 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 9.4 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H), 5.34 (br. s, 1 H), 4.55–4.40 (m, 6 H), 4.11 (dd, *J* = 5.6, 2.4 Hz, 1 H), 4.09 (t, *J* = 2.4 Hz, 1 H), 3.92–3.87 (m, 1 H), 3.82 (dd, *J* = 7.6, 4.7 Hz, 1 H), 3.73–3.68 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 137.6, 137.3, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 82.4, 82.2, 73.5, 72.4 (q, $^2J_{(C–F)}$ = 28 Hz), 72.0, 68.9, 65.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –72.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3712, 3363, 3013, 2926, 2862, 2343, 2102, 1454, 1364, 1280, 1217, 1166, 1096, 1027, 698, 670 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_4$ $(M + 1)^+$ 488.2049; found 488.2060.

(2*S*,3*R*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidin-1-ol (20): Following the general procedure, starting from nitrone **17** (100 mg, 0.24 mmol) and trimethyl(trifluoromethyl)silane (**10**; 34 mg, 0.24 mmol), product **20** was obtained as a white solid (80 mg, 69%) after purification by silica gel column chromatography (12% ethyl acetate/hexanes). R_f = 0.6 (20% ethyl acetate/hexanes), m.p. 87–88 °C. $[\alpha]_D^{20}$ = –10.5 (*c* = 2.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 15 H), 5.99 (s, 1 H), 4.73, 4.58 (ABq, *J* = 11.7 Hz, 2 H), 4.55–4.47 (m, 4 H), 4.07 (t, *J* = 3.8 Hz, 1 H), 4.00–3.88 (m, 4 H), 3.45 (dd, *J* = 9.7, 6.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.8, 137.2, 128.6, 128.5, 128.1, 128.0, 127.9, 127.9, 79.1, 74.7, 74.4, 74.1, 73.8 (q, $^2J_{(C–F)}$ = 28 Hz), 73.7, 73.6, 73.1, 67.4, 65.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.6 ppm. IR (KBr): $\tilde{\nu}$ = 3712, 3318, 3029, 2932, 2873, 2346, 2101, 1457, 1368, 1271, 1235, 1177, 1142, 1114, 1054, 1028, 908, 695 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_4$ $(M + 1)^+$ 488.2049; found 488.2040.

(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidin-1-ol (21): Following the general procedure, starting from nitrone *ent*-**13** (100 mg, 0.24 mmol) and trimethyl(trifluoromethyl)silane (**10**; 34 mg, 0.24 mmol), product **21** was obtained as a colorless oil (70 mg, 60%) after purification by silica gel column chromatography (12% ethyl acetate/hexanes). R_f = 0.6 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –10.5 (*c* = 2.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 15 H), 5.60 (s, 1 H), 4.59–4.40 (m, 6 H), 4.13–4.09 (m, 2 H), 3.90 (dd, *J* = 12.7, 8.1 Hz, 1 H), 3.83 (dd, *J* = 7.6, 4.6 Hz, 1 H), 3.81–3.70 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.6, 137.3, 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 127.9, 127.8, 82.4, 82.2, 73.5, 72.7, 72.4, 72.1, 72.0 (q, $^2J_{(C–F)}$ = 28 Hz), 68.9, 65.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –72.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3736, 3339, 3032, 2930, 2859, 2343, 2102, 1455, 1364, 1277, 1216, 1167, 1100, 1028, 698 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_4$ $(M + 1)^+$ 488.2049; found 488.2037.

(2*S*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidin-1-ol (22): Following the general procedure, starting from nitrone **18** (100 mg, 0.24 mmol) and trimethyl(trifluoromethyl)silane (**10**; 34 mg, 0.24 mmol), product **22** was obtained as a colorless oil (65 mg, 56%) after purification by silica gel column chromatography (12% ethyl acetate/hexanes). R_f = 0.6 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 17.7 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 15 H), 5.60 (s, 1 H), 4.59–4.40 (m, 6 H), 4.13–4.09 (m, 2 H), 3.90 (dd, *J* = 12.7, 8.1 Hz, 1 H), 3.83 (dd, *J* = 7.6, 4.6 Hz, 1 H), 3.81–3.70 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 137.6, 137.0, 128.6, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 80.1, 79.1, 75.4, 75.1, 74.8, 74.5 (q, $^2J_{(C–F)}$ = 28.7 Hz), 73.7, 72.1, 71.7, 69.5, 67.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3732, 3375, 2926, 2856, 2397, 2104, 1658, 1455, 1276, 1217, 1126, 1028, 698 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_4$ $(M + 1)^+$ 488.2049; found 488.2054.

(3a*S*,4*S*,6*S*,6a*R*)-4-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-6-(trifluoromethyl)dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5(4*H*)-ol (23): Following the general procedure, starting from nitrone **19** (100 mg, 0.39 mmol) and trimethyl(trifluoromethyl)silane (**10**; 56 mg, 0.39 mmol), product **23** was obtained as a colorless oil (80 mg, 63%) after purification by silica gel column chromatography (12% ethyl acetate/hexanes). R_f = 0.7 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –24.4 (*c* = 2.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (s, 1 H), 4.51 (dd, *J* = 6.9, 4.4 Hz, 1 H), 4.32 (dd, *J* = 12.2, 5.6 Hz, 2 H), 4.08 (dd, *J* = 8.9, 6.6 Hz, 1 H), 3.99 (dd, *J* = 8.9, 4.7 Hz, 1 H), 3.70–3.64 (m, 1 H), 3.26 (t, *J* = 5.5 Hz, 1 H), 1.56 (s, 3 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.1, 126.3, 123.5, 120.8 (q, $^1J_{(C–F)}$ = 277.7 Hz), 114.4, 110.3, 109.9, 76.4, 76.4, 76.1, 74.4, 73.3, 73.0, 72.8, 72.5 (q, $^2J_{(C–F)}$ = 28.3 Hz), 66.0, 27.4, 26.3, 25.3, 25.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3715, 3429, 2991, 2937, 1670, 1460, 1384, 1336, 1270, 1216, 1155, 1074, 927, 890, 850, 697 cm^{-1}. HRMS: calcd. for $C_{13}H_{20}F_3NO_5$ $(M + 1)^+$ 328.1372; found 328.1375.

General Procedure for the Cleavage of N–O Bond: Zn powder (40 mmol) and indium powder (0.01 mmol) were added to a solution of cyclic hydroxylamine (1 mmol) in a saturated solution of NH_4Cl and MeOH (1:0.8, 30 mL) and the mixture was heated to 70 °C. After 12 h, the mixture was cooled to room temperature, and the solvent was evaporated to obtain the residue. Then, EtOAc was added to the residue and washed with an aqueous solution of Na_2CO_3. The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to obtain the crude product, which was purified by basic alumina flash column chromatography.

(2*S*,3*S*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidine (15): Following the general procedure, starting from cyclic hydroxylamine **14** (30 mg, 0.06 mmol), product **15** was obtained as a colorless oil (26 mg, 90%) after purification by basic alumina column chromatography (8% ethyl acetate/hexanes). R_f = 0.7 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –8.9 (*c* = 2.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 15 H), 4.62–4.42 (m, 6 H), 4.25 (t, *J* = 4.4 Hz, 1 H), 4.00 (dd, *J* = 7.4, 4.7 Hz, 1 H), 3.66 (dd, *J* = 8.5, 3.9 Hz, 1 H), 3.60 (dd, *J* = 9.7, 3.4 Hz, 1 H), 3.49 (dd, *J* = 9.7, 4.7 Hz, 1 H), 3.35–3.34 (m, 1 H), 2.17 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.9, 137.5, 128.6, 128.6, 128.6, 128.1, 128.0, 128.0, 127.9, 85.2, 84.9, 82.4, 73.4, 72.6, 72.6, 68.3, 63.6, 63.3 (q, $^2J_{(C–F)}$ = 30 Hz), 61.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3363, 3013, 2926, 2862, 2343, 2102, 1454, 1364, 1280, 1217, 1166, 1096, 1027, 698, 670 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_3$ $(M + 1)^+$ 472.2100; found 472.2099.

(2*S*,3*R*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidine (24): Following the general procedure, starting from cyclic hydroxylamine **20** (30 mg, 0.06 mmol), product **24** was obtained as a colorless oil (24 mg, 83%) after purification by basic alumina column chromatography (8% ethyl acetate/hexanes). R_f = 0.7 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –21.7 (*c* = 2.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 15 H),

4.66 (d, J = 11.6 Hz, 1 H), 4.58–4.47 (m, 5 H), 4.08–4.03 (m, 2 H), 3.73 (dd, J = 7.9, 4.4 Hz, 1 H), 3.70–3.63 (m, 2 H), 3.53–3.45 (m, 1 H), 2.27 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 138.1, 137.5, 128.6, 128.5, 128.0, 127.9, 127.9, 79.2, 78.2, 73.8, 73.4, 73.4, 72.8, 69.0, 62.8, 62.5, 62.2, 61.9 (q, $^2J_{(C–F)}$ = 29.3 Hz), 59.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3362, 3029, 2925, 2857, 2328, 1651, 1455, 1370, 1279, 1217, 1158, 1123, 1112, 915, 698 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_3$ (M + 1)$^+$ 472.2100; found 472.2090.

(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidine (25): Following the general procedure, starting from cyclic hydroxylamine **21** (30 mg, 0.06 mmol), product **25** was obtained as a colorless oil (27 mg, 93%) after purification by basic alumina column chromatography (8% ethyl acetate/hexanes). R_f = 0.7 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 18.4 (c = 2.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 1 H), 4.62–4.42 (m, 6 H), 4.25 (t, J = 4.4 Hz, 1 H), 4.00 (dd, J = 7.6, 4.8 Hz, 1 H), 3.64 (bd, J = 4.9 Hz, 1 H), 3.60 (dd, J = 9.7, 3.4 Hz, 1 H), 3.49 (dd, J = 9.7, 4.6 Hz, 1 H), 3.34 (br. s, 1 H), 2.55 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.9, 137.5, 128.6, 128.6, 128.5, 128.1, 128.0, 128.0, 128.0, 85.2, 84.9, 73.4, 72.6, 72.6, 68.4, 63.6, 63.3 (q, $^2J_{(C–F)}$ = 29 Hz), 61.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3347, 3064, 3032, 2917, 2862, 2109, 1496, 1454, 1363, 1279, 1208, 1163, 1134, 1108, 1028, 912, 858, 698 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_3$ (M + 1)$^+$ 472.2100; found 472.2098.

(2*S*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trifluoromethyl)pyrrolidine (26): Following the general procedure, starting from cyclic hydroxylamine **22** (30 mg, 0.06 mmol), product **26** was obtained as a colorless oil (25 mg, 86%) after purification by basic alumina column chromatography (8% ethyl acetate/hexanes). R_f = 0.7 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 13.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 15 H), 4.58–4.40 (m, 6 H), 4.07 (dd, J = 3.4, 1.2 Hz, 1 H), 3.91 (d, J = 2.0 Hz, 1 H), 3.74 (dd, J = 8.6, 4.7 Hz, 1 H), 3.69–3.62 (m, 3 H), 3.59 (dd, J = 7.3, 4.7 Hz, 1 H), 2.30 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 137.9, 137.4, 128.6, 128.6, 128.1, 128.0, 127.9, 127.8, 127.8, 82.5, 81.8, 73.7, 72.0, 71.7, 69.8, 65.6, 65.3, 65.0, 64.7 (q, $^2J_{(C–F)}$ = 30 Hz), 60.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3736, 3280, 3032, 2932, 2860, 2361, 1657, 1455, 1405, 1086, 1052, 1028, 697 cm^{-1}. HRMS: calcd. for $C_{27}H_{28}F_3NO_3$ (M + 1)$^+$ 472.2100; found 472. 2085.

(3a*S*,4*S*,6*S*,6a*R*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-6-(trifluoromethyl)tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (27): Following the general procedure, starting from cyclic hydroxylamine **23** (30 mg, 0.09 mmol), product **27** was obtained as a colorless oil (22 mg, 77%) after purification by basic alumina column chromatography (6% ethyl acetate/hexanes). R_f = 0.8 (20% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –19.3 (c = 2.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 (dd, J = 6.7, 3.5 Hz, 1 H), 4.29 (t, J = 6.2 Hz, 1 H), 4.11–4.04 (m, 2 H), 3.86–3.81 (m, 1 H), 3.74 (bt, J = 3.3 Hz, 1 H), 3.24 (br. s, 1 H), 2.38 (br. s, 1 H), 1.53 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.5, 123.8 (q, $^1J_{(C–F)}$ = 277 Hz), 114.5, 109.7, 80.8, 80.0, 79.9, 78.1, 66.6, 66.2, 64.8, 64.6, 64.2, 64.0 (q, $^2J_{(C–F)}$ = 29.3 Hz), 27.5, 26.8, 25.4, 25.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3366, 2990, 2938, 1661, 1457, 1383, 1375, 1292, 1271, 1216, 1158, 1141, 1071, 969, 889, 853, 693 cm^{-1}. HRMS: calcd. for $C_{13}H_{20}F_3NO_4$ (M + 1)$^+$ 312.1423; found 312.1423.

General Procedure for Hydrogenolysis: To a solution of cyclic hydroxylamine (1.00 mmol) in MeOH was added 10% $Pd(OH)_2$/C (150 mg) at room temperature under N_2. Then, the reaction flask was purged with H_2 followed by addition of 10 drops of conc. HCl, and the reaction mixture was stirred for 24 h at room temperature under H_2 atmosphere. The mixture was then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in a minimum amount of H_2O and stirred with IRA-400 resin (OH^- form) until it reached pH 11. After filtration, the filtrate was concentrated in vacuo to give pure trifluoromethylated polyhydroxylated pyrrolidine.

(2*S*,3*S*,4*S*,5*R*)-2-(Hydroxymethyl)-5-(trifluoromethyl)pyrrolidine-3,4-diol (16): Following the general procedure, starting from cyclic hydroxylamine **14** (80 mg, 0.16 mmol), product **16** was obtained as a white solid (31 mg, 95%). R_f = 0.4 (100% ethyl acetate), m.p. 159–160 °C. $[\alpha]_D^{20}$ = –4.1 (c = 2.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.24 (t, J = 7.2 Hz, 1 H), 3.87 (t, J = 8.2 Hz, 1 H), 3.75–3.66 (m, 2 H), 3.63 (t, J = 7.8 Hz, 1 H), 2.95–2.93 (m, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 127.3, 124.5 (q, $^1J_{(C–F)}$ = 277 Hz), 76.5, 68.4, 61.6, 61.4, 61.3, 61.0, 60.7 (q, $^2J_{(C–F)}$ = 29 Hz), 59.6 ppm. ^{19}F NMR (376 MHz, D_2O): δ = –75.8 ppm. IR (KBr): $\tilde{\nu}$ = 3366, 2924, 2868, 1657, 1455, 1261, 1186, 1029, 976, 823, 751 cm^{-1}. HRMS: calcd. for $C_6H_{10}F_3NO_3$ (M + 1)$^+$ 202.0691; found 202.0694.

(2*S*,3*R*,4*S*,5*R*)-2-(Hydroxymethyl)-5-(trifluoromethyl)pyrrolidine-3,4-diol (28): Following the general procedure, starting from cyclic hydroxylamine **20** (90 mg, 0.18 mmol), product **28** was obtained as a colorless oil (36 mg, 94%). R_f = 0.4 (100% ethyl acetate). $[\alpha]_D^{20}$ = –5.9 (c = 2.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.41 (dd, J = 7.5, 4.1 Hz, 1 H), 4.14 (t, J = 3.1 Hz, 1 H), 3.76 (dd, J = 11.3, 6.9 Hz, 1 H), 3.68–3.61 (m, 2 H), 3.18 (td, J = 6.4, 2.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 130.5, 127.7, 125.0, 122.2 (q, $^1J_{(C–F)}$ = 277 Hz), 73.0, 72.2, 62.4, 62.1, 61.9, 61.6, 61.3 (q, $^2J_{(C–F)}$ = 29 Hz), 60.8, 59.3 ppm. ^{19}F NMR (376 MHz, D_2O): δ = –75.4 ppm. IR (neat): $\tilde{\nu}$ = 3363, 2924, 2851, 1656, 1452, 1262, 1020, 913, 826, 757 cm^{-1}. HRMS: calcd. for $C_6H_{10}F_3NO_3$ (M + 1)$^+$ 202.0691; found 202.0687.

(2*R*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-(trifluoromethyl)pyrrolidine-3,4-diol (29): Following the general procedure, starting from cyclic hydroxylamine **21** (80 mg, 0.16 mmol), product **29** was obtained as a colorless oil (29 mg, 92%). R_f = 0.4 (100% ethyl acetate). $[\alpha]_D^{20}$ = 3.5 (c = 2.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.21 (t, J = 7.3 Hz, 1 H), 3.84 (t, J = 8.0 Hz, 1 H), 3.71 (s, 1 H), 3.69–3.66 (m, 1 H), 3.64–3.58 (m, 1 H), 3.06–2.89 (m, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 130.1, 127.3, 124.4, 122.1 (q, $^1J_{(C–F)}$ = 277 Hz), 76.6, 66.5, 61.7, 61.5, 61.4, 61.1, 60.8 (q, $^2J_{(C–F)}$ = 29 Hz), 59.7 ppm. ^{19}F NMR (376 MHz, D_2O): δ = –75.9 ppm. IR (neat): $\tilde{\nu}$ = 3467, 2925, 1655, 1454, 1284, 1215, 940, 760, 695 cm^{-1}. HRMS: calcd. for $C_6H_{10}F_3NO_3$ (M + 1)$^+$ 202.0691; found 202.0696.

(2*S*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-(trifluoromethyl)pyrrolidine-3,4-diol (30): Following the general procedure, starting from cyclic hydroxylamine **22** (60 mg, 0.12 mmol), product **30** was obtained as a white solid (22 mg, 88%). R_f = 0.4 (100% ethyl acetate), m.p. 172–173 °C. $[\alpha]_D^{20}$ = 4.8 (c = 2.00, H_2O). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.35 (d, J = 2.4 Hz, 1 H), 4.14 (s, 1 H), 4.07 (dd, J = 8.4, 2.3 Hz, 1 H), 4.04–3.93 (m, 2 H), 3.85–3.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 125.8, 123.0 (q, $^1J_{(C–F)}$ = 276 Hz), 77.4, 76.4, 68.0, 67.7, 67.5, 67.3, 67.0 (q, $^2J_{(C–F)}$ = 32.7 Hz) ppm. ^{19}F NMR (376 MHz, CD_3OD): δ = –72.2 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 2928, 2868, 1661, 1459, 1261, 1109, 802, 765, 716 cm^{-1}. HRMS: calcd. for $C_6H_{10}F_3NO_3$ (M + 1)$^+$ 202.0691; found 202.0691.

(2*S*,3*S*,4*R*,5*S*)-2-[(*S*)-1,2-Dihydroxyethyl]-5-(trifluoromethyl)-pyrrolidine-3,4-diol (31): To a solution of trifluoromethylated amine

27 (80 mg, 0.26 mmol) in MeOH (2.5 mL) was added aq. HCl (6 N, 2.5 mL) at room temperature and stirred for 24 h. Then the solvent was removed in vacuo, and the residue was dissolved in minimum amount of H_2O and stirred with IRA-400 resin (OH^- form) until pH 11. After filtration, the filtrate was concentrated in vacuo to give pure trifluoromethylated polyhydroxylated pyrrolidine **31** as colorless oil (29 mg, 85%). R_f = 0.3 (100% ethyl acetate). $[a]_D^{20}$ = –12.6 (c = 1.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.28 (dd, J = 5.2, 4.3 Hz, 1 H), 3.98 (t, J = 6.2 Hz, 1 H), 3.73–3.63 (m, 3 H), 3.59–3.52 (m, 1 H), 3.17 (dd, J = 6.7, 4.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 129.7, 126.9, 124.1, 121.4 (q, $^1J_{(C-F)}$ = 277.7 Hz), 72.0, 71.8, 70.9, 63.6, 63.3. 63.0 (q, $^2J_{(C-F)}$ = 29 Hz), 62.4 ppm. ^{19}F NMR (376 MHz, D_2O): δ = –75.2 ppm. IR (neat): $\tilde{\nu}$ = 3437, 2924, 2857, 1658, 1455, 1262, 1146, 1093, 1016, 970, 875, 800, 751 cm^{-1}. HRMS: calcd. for $C_7H_{12}F_3NO_4$ $(M + 1)^+$ 232.0797; found 232.0798.

Supporting Information (see footnote on the first page of this article): Characterization data including ^{1}H, ^{13}C NMR and ^{19}F NMR spectra for all compounds.

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[1] a) O. R. Martin, *Ann. Pharm. Fr.* **2007**, *65*, 5–13; b) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295; c) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; d) A. Mitchinson, A. Nadin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862–2892; e) A. B. Mauger, *J. Nat. Prod.* **1996**, *59*, 1205–1211; f) T. Shibata, O. Nakayama, Y. Tsurumi, M. Okuhara, H. Terano, M. Kohsaka, *J. Antibiot.* **1988**, *41*, 296–301; g) R. J. Nash, E. A. Bell, J. M. Williams, *Phytochemistry* **1985**, *24*, 1620–1622; h) D. W. C. Jones, R. J. Nash, E. A. Bell, J. M. Williams, *Tetrahedron Lett.* **1985**, *26*, 3125–3126; i) J. Furukawa, S. Okuda, K. Saito, S.-I. Hatanaka, *Phytochemistry* **1985**, *24*, 593–594; j) A. Welter, J. Jadot, G. Dardenne, M. Marlier, J. Casimir, *Phytochemistry* **1976**, *15*, 747–749; k) B. A. Sobin, F. W. Tanner Jr., *J. Am. Chem. Soc.* **1954**, *76*, 4053.

[2] a) P. Compain, O. R. Martin, *Iminosugars: From Synthesis to Therapeutic Applications*, Wiley, Chichester, UK, **2007**; b) N. Asano, *Glycobiology* **2003**, *13*, 93R–104R; c) Y. Nishimura, *Curr. Top. Med. Chem.* **2003**, *3*, 575–591; d) A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, Germany, **1999**; e) G. S. Jacob, *Curr. Op. Struct. Biol.* **1995**, *5*, 605–611.

[3] a) H. Fiaux, D. A. Kuntz, D. Hoffman, R. C. Janzer, S. Gerber-Lemaire, D. R. Rose, L. Juillerat-Jeanneret, *Bioorg. Med. Chem.* **2008**, *16*, 7337–7346; b) S. D. Naik, R. Y. Ambaye, S. V. Gokhale, *Anticancer Res.* **1987**, *7*, 87–90.

[4] a) Y. Tanaka, J. Kato, M. Kohara, M. S. Galinski, *Antiviral Res.* **2006**, *72*, 1–9; b) I. Robina, A. J. Moreno-Vargas, A. T. Carmona, P. Vogel, *Curr. Drug Metab.* **2004**, *5*, 329–361; c) N. Asano, M. Nishida, A. Kato, H. Kizu, K. Matsui, Y. Shimada, T. Itoh, M. Baba, A. A. Watson, R. J. Nash, P. M. de Lilley, D. J. Watkin, G. W. J. Fleet, *J. Med. Chem.* **1998**, *41*, 2565–2571.

[5] K. A. Watson, E. P. Mitchell, L. N. Johnson, J. C. Son, C. J. F. Bichard, M. G. Orchard, G. W. J. Fleet, N. G. Oikonomakos, D. D. Leonidas, M. Kontou, A. Papageorgioui, *Biochemistry* **1994**, *33*, 5745–5758.

[6] W. Meutermans, G. T. Le, B. Becker, *ChemMedChem* **2006**, *1*, 1164–1194.

[7] a) S. F. Matkhalikova, V. M. Malikov, S. Y. Yunusov, *Khim. Prir. Soedin.* **1969**, *5*, 606–607; b) S. F. Matkhalikova, V. M. Malikov, S. Y. Yunusov, *Khim. Prir. Soedin.* **1969**, *5*, 30–32.

[8] a) K. Yasuda, H. Kizu, T. Yamashita, Y. Kameda, A. Kato, R. J. Nash, G. W. J. Fleet, R. J. Molyneux, N. Asano, *J. Nat. Prod.* **2002**, *65*, 198–202; b) R. J. Molyneux, Y. T. Pan, J. E. Tropea, A. D. Elbein, C. H. Lawyer, D. J. Hughes, G. W. J. Fleet, *J. Nat. Prod.* **1993**, *56*, 1356–1364.

[9] a) P. D. O'Shea, C.-y. Chen, D. Gauvreau, F. Gosselin, G. Hughes, C. Nadeau, R. P. Volante, *J. Org. Chem.* **2009**, *74*, 1605–1610; b) S. Léger, C. I. Bayly, W. C. Black, S. Desmarais, J.-P. Falgueyret, F. Massé, M. D. Percival, J.-F. Truchon, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4328–4332; c) G. L. Grunewald, J. Lu, K. R. Criscione, C. O. Okoro, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5319–5323; d) N. C. Yoder, K. Kumar, *Chem. Soc. Rev.* **2002**, *31*, 335–341; e) A. Sutherland, C. L. Willis, *Nat. Prod. Rep.* **2000**, *17*, 621–631; f) W. S. Faraci, C. T. Walsh, *Biochemistry* **1989**, *28*, 431–437.

[10] a) R. Smits, C. D. Cadicamoo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727–1739; b) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029; c) W. R. Dolbier Jr., *J. Fluorine Chem.* **2005**, *126*, 157–163; d) X.-L. Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711–6745.

[11] a) A. Bandaru, K. P. Kaliappan, *Synlett* **2012**, *23*, 1473–1476; b) R. K. Khangarot, K. P. Kaliappan, *Eur. J. Org. Chem.* **2011**, 6117–6127; c) K. P. Kaliappan, P. Das, S. T. Chavan, S. G. Sabharwal, *J. Org. Chem.* **2009**, *74*, 6266–6274; d) K. P. Kaliappan, P. Das, *Synlett* **2008**, 841–844.

[12] S. A. Pujari, K. P. Kaliappan, A. Valleix, D. Grée, R. Grée, *Synlett* **2008**, 2503–2507.

[13] a) W. Zhang, K. Sato, A. Kato, Y.-M. Jia, X.-G. Hu, F. X. Wilson, R. v. Well, G. Horne, G. W. J. Fleet, R. J. Nash, C.-Y. Yu, *Org. Lett.* **2011**, *13*, 4414–4417; b) I. Delso, T. Tejero, A. Goti, P. Merino, *J. Org. Chem.* **2011**, *76*, 4139–4143; c) I. Delso, E. Marca, V. Mannucci, T. Tejero, A. Goti, P. Merino, *Chem. Eur. J.* **2010**, *16*, 9910–9919; d) M. Marradi, S. Cicchi, J. I. Delso, L. Rosi, T. Tejero, P. Merino, A. Goti, *Tetrahedron Lett.* **2005**, *46*, 1287–1290; e) P. Merino, J. Revuelta, T. Tejero, S. Cicchi, A. Goti, *Eur. J. Org. Chem.* **2004**, 776–782; f) P. Merino, T. Tejero, J. Revuelta, P. Romero, S. Cicchi, V. Mannucci, A. Brandi, A. Goti, *Tetrahedron: Asymmetry* **2003**, *14*, 367–379; g) M. Lombardo, S. Fabbroni, C. Trombini, *J. Org. Chem.* **2001**, *66*, 1264–1268; h) R. Ballini, E. Marcantoni, M. Petrini, *J. Org. Chem.* **1992**, *57*, 1316–1318.

[14] a) G. K. S. Prakash, S. Chacko, *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793–802, and references cited therein; b) N. Shibata, S. Mizuta, H. Kawai, *Tetrahedron: Asymmetry* **2008**, *19*, 2633–2644; c) G. K. S. Prakash, M. Mandal, G. A. Olah, *Angew. Chem.* **2001**, *113*, 609–610; *Angew. Chem. Int. Ed.* **2001**, *40*, 589–590; d) G. K. S. Prakash, M. Mandal, *J. Fluorine Chem.* **2001**, *112*, 123–131; e) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786; f) R. Krishnamurti, D. R. Bellew, G. K. S. Prakash, *J. Org. Chem.* **1991**, *56*, 984–989; g) G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393–395; h) I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.* **1984**, *25*, 2195–2198.

[15] a) N. Allendörfer, M. Es-Sayed, M. Nieger, S. Bräse, *Tetrahedron Lett.* **2012**, *53*, 388–391; b) R. Kowalczyk, A. J. F. Edmunds, R. G. Hall, G. Bolm, *Org. Lett.* **2011**, *13*, 768–771; c) N. E. Shevchenko, K. Vlasov, V. G. Nenajdenko, G.-V. Röschenthaler, *Tetrahedron* **2011**, *67*, 69–74; d) A. D. Dilman, D. E. Arkhipov, V. V. Levin, P. A. Belyakov, A. A. Korlyukov, M. I. Struchkova, V. A. Tartakovsky, *J. Org. Chem.* **2000**, *65*, 8848–8856; e) J.-C. Blazejewski, E. Anselmi, M. P. Wilmshurst, *Tetrahedron Lett.* **1999**, *40*, 5475–5478; f) Y. Yokoyama, K. Mochida, *Tetrahedron Lett.* **1997**, *38*, 3443–3446. For reviews on trifluoromethylation with Me_3SiCF_3, see: g) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; h) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613–7632.

[16] a) Y. Chuyi, L. Yixian, J. Yuemei, *Faming Zhuanli Shenqing* **2011**, CN 102199116 A 20110928; b) D. W. Nelson, J. Owens, D. Hiraldo, *J. Org. Chem.* **2001**, *66*, 2572–2582; c) D. W. Nelson, R. A. Easley, B. N. V. Pintea, *Tetrahedron Lett.* **1999**, *40*, 25–28.

[17] a) E.-L. Tsou, S.-Y. Chen, M.-H. Yang, S.-C. Wang, T.-R. R. Cheng, W.-C. Cheng, *Bioorg. Med. Chem.* **2008**, *16*, 10198–10204; b) P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marradi, E. Faggi, C. Parmeggiani, A. Goti, *Eur. J. Org. Chem.* **2008**, 2929–2947; c) P. Merino, I. Delso, T. Tejero, F. Cardona, A. Goti, *Synlett* **2007**, 2651–2654; d) C.-Y. Yu, M.-H. Huang, *Org. Lett.* **2006**, *8*, 3021–3024; e) M. K. Gurjar, R. G. Borhade, V. G. Puranik, C. V. Ramana, *Tetrahedron Lett.* **2006**, *47*, 6979–6981; f) A. Toyao, O. Tamura, H. Takagi, H. Ishibashi, *Synlett* **2003**, 35–38.

[18] S. Cicchi, M. Bonanni, F. Cardona, J. Revuelta, A. Goti, *Org. Lett.* **2003**, *5*, 1773–1776.

[19] a) P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marradi, E. Faggi, C. Parmeggiani, A. Goti, *Eur. J. Org. Chem.* **2008**, 2929–2947; b) P. Merino, I. Delso, T. Tejero, F. Cardona, A. Goti, *Synlett* **2007**, 2651–2654.

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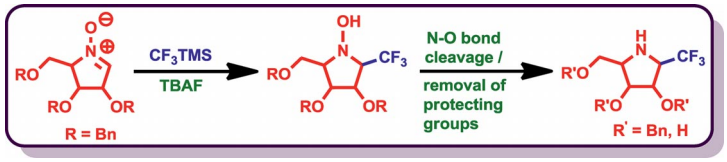

An efficient strategy for the synthesis of a variety of trifluoromethylated polyhydroxypyrrolidines is described. This strategy involves a diastereoselective nucleophilic addition reaction of trimethyl(trifluoromethyl)silane to sugar-derived cyclic nitrones followed by reductive N–O bond cleavage and removal of benzyl groups.

Stereoselective Synthesis

Keywords: Synthetic methods / Nitrogen heterocycles / Fluorine / Nucleophilic addition / Diastereoselectivity

